FDA CASE STUDY

A young company seeks advice from FDA

SEEKING EARLY FEEDBACK FROM FDA THROUGH THE PRE-SUBMISSION PROGRAM

THIS FICTIONALIZED CASE STUDY IS THE SEVENTH IN AN EDUCATIONAL SERIES PUBLISHED BY THE U.S. FOOD AND DRUG ADMINISTRATION.

Improved Monitoring of Multiple Myeloma

Chica Morales walked into the lobby of Watson and Rimando Consulting, excitement punctuating her every step. A recent graduate with an MS in Biotechnology and an MBA, Morales had combined her two passions into the recent launch of a start-up medical device company called Ig Medical. Today, she and a small team of her associates were seeking assistance with developing their regulatory strategy for their first product: an in vitro diagnostic (IVD) medical device called "IgTope" that measures changes in antibody levels in patients previously diagnosed with multiple myeloma. (Appendix A)

After a brief wait, Morales and her team were ushered into a small conference room. Waiting for them were Joe Watson, a veteran attorney with a specialty in regulatory affairs; Pepper Pans, a dynamic young employee who had just joined the consulting company after completing a fellowship with the FDA; and Dr. Carly Johnson, a statistician specializing in preclinical study designs for medical devices.

"Well, we are excited to have you and your team here with us this morning, Ms. Morales," Watson began after everyone was seated. "We look forward to helping you get your product to market. We've looked through the initial information you provided, but could you give us a little more background on IgTope and the goals of your company to make sure we are all on the same page?"

"Of course," Morales answered. "Ig Medical is focused on improving the detection and monitoring of multiple myeloma (MM). I first got interested in helping those with MM due to the struggles my father had with the disease.

"MM is a type of cancer that starts in the plasma cells within bone marrow. It leads to a reduction in both red and white blood cells, leaving patients fatigued and susceptible to infection. As the cancer progresses in the bone marrow, it commonly causes pain in affected bones such as the ribs and spine. Over time, the cancer cells can weaken affected bones and lead to an increased risk of fractures when a patient performs normal every day activities. (Appendix A)

"IgTope is an in vitro diagnostic device that will improve the monitoring of MM by measuring changes in the types of antibodies a patient produces," Morales stated with an air of pride. (Exhibit 1)

"Currently, there is one set of cleared devices, Hevylite®, similar to IgTope that we have found in FDA's premarket notification database," said Morales. Pausing briefly, she handed the consultants a printout of a table. "Due to the similarities between the Hevylite® and IgTope products and their intended use, we believe that Hevylite® can serve as a substantially equivalent predicate for IgTope (Table 1), and that we should be able to submit a premarket notification, or 510(k), for clearance to market our device."

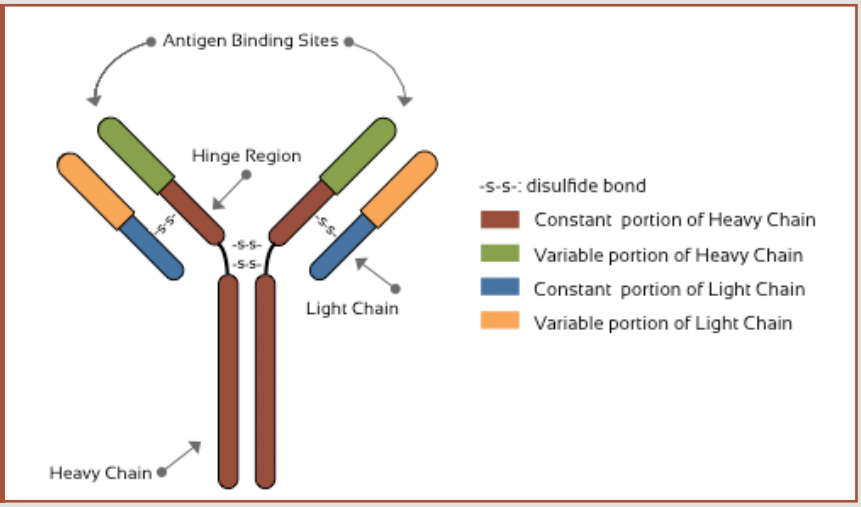
Watson was impressed. "It sounds like you have a very useful product that will improve the treatment of patients with MM. And it seems like you already have an idea of how to obtain clearance to market your device from FDA. What specifically can we help you with today?"

EXHIBIT 1: HOW IGTOPE WORKS

Antibodies are made of two basic structural units, heavy chains and light chains (Figure 1). There are several different types of antibody heavy chains (e.g., alpha, gamma, mu). Antibodies are grouped together based on which heavy chain is present. For example, if the heavy chain gamma is present, the antibody is of the immunoglobulin gamma (IgG) isotype. In humans, these heavy chains connect to two types of light chains called lambda (κ) and kappa (λ) to form the final antibody molecule.

FIGURE 1: REPRESENTATION OF A TYPICAL IGG ANTIBODY MOLECULE

Figure 1: The IgTope device forms a complex with tumor-produced IgG by binding to junctional epitopes between the heavy chain and light chains on tumor-produced IgG (i.e., where the dark blue and gold regions connect through disulfide bonding [-s-s-]).



Specifically, IgTope quantifies the ratio of IgGκ to IgGλ produced by a patient using a nephlometric assay (measurement of the light scattered in a turbid sample; see Appendix B). The ratio of IgGκ to IgGλ produced by the immunoglobulin-synthesizing healthy plasma cells is very consistent. However, in patients with MM, the ratio becomes significantly skewed from that of the normal population. Therefore, the IgGκ to IgGλ ratio is a useful biomarker for monitoring previously diagnosed IgG MM patients to evaluate disease progression over time.

Serum protein electrophoresis (SPE) with scanning densitometry and/or immunofixation electrophoresis (IFE) are typical analytical tests for gammopathies (disturbances in immunoglobulin synthesis). However, these are mostly qualitative assays and are not sensitive enough to provide a good assay for monitoring MM.

Nephelometry, the basis of the IgTope system, is an alternative technique used routinely for immunoglobulin measurements and is analytically quantifiable down to low concentrations. Patient samples normally contain large amounts of non-tumor produced IgG. In the case of MM patients, normal immunoglobulin can mask subtle changes in tumor-produced monoclonal IgG. Therefore, to provide a method for monitoring MM progression, a quantitative technique paired with a specific assay that can help distinguish abnormal IgG produced by a patient's tumor is needed.

IgTope provides a way to quantifiably measure tumor-produced IgG κ and λ by binding an antibody that is specific to junctional epitopes between the heavy chain and light chains on IgG. After binding, IgTope and the patient's IgG form a complex that is easily quantifiable using nephelometry, and it is possible to look at the kappa/lambda ratio and identify an abnormal population without significant interference from IgG produced by their healthy plasma cells.

Table 1. Comparison of IgTope to Potential Predicate and Reference Devices

Feature	Hevylite® IgG Proposed Predicate	Hevylite® IgA Additional Reference Device	Hevylite® IgM Additional Reference Device	IgTope
Device Description	A quantitative in vitro assay for the measurement of IgGκ and IgGλ in serum. IgGκ/λ ratio can be used to monitor previously diagnosed MM.	A quantitative in vitro assay for the measurement of IgAκ and IgAλ in serum. IgAκ/λ ratio can be used to monitor previously diagnosed MM.	A quantitative in vitro assay for the measurement of IgMκ and IgMλ in serum.	A quantitative in vitro assay for the measurement of IgGκ and IgGλ in serum. The IgGκ/λ ratio can be used to monitor previously diagnosed MM.
Immunoglobulin Measured	IgGκ and IgGλ	IgAκ and IgAλ	IgMκ and IgMλ	IgGκ and IgGλ
Measurement Platform(s)	Siemens BN II	Siemens BN II	Siemens BN II and SPA_{PLUS}	Custom Nephlometer (IgNepholmeter)
Regulatory Submissions	K132555	K082823 and K140105	K113823 and K140686	N/A
Product Codes	PCN, PCO (21 CFR 866.5510)	OPX, OPY (21 CFR 866.5510)	PDE, PDF (21 CFR 866.5510)	Proposed: PCN, PCO (21 CFR 866.5510)

Planning Product Development with an Eye to Regulatory Requirements

"We'd like your help with planning the tests we'll need to conduct to bring IgTope to the market," the founder of Ig Medical responded. "We recently began working with a local patent attorney to help safeguard our intellectual property. They recommended that we meet with you to discuss how to begin interacting with FDA to make sure that we meet the Agency's regulatory requirements and expectations for marketing our device."

"I applaud your foresight. It's much easier to do things correctly from the beginning than to try and satisfy FDA's expectations further down the line. Where are you currently with IgTope's development?" Watson asked.

"We have a number of prototype systems developed and we'd like to begin the analytical bench testing and any necessary clinical testing needed to get a 510(k) clearance. We would love to receive your guidance on how to design the nonclinical (e.g., analytical performance) testing first, and at a later point, the clinical studies," Morales replied.

"We can provide you with substantial assistance in those areas," Watson smiled and turned to his colleague. "Dr. Johnson is our expert on the design of analytical performance validation studies and she has some background in clinical trials. She has helped design studies for a number of IVD devices and should be able to guide you through the process.

In Vitro Diagnostic Devices

Taking the lead, Johnson began, "Things may seem a little daunting at this stage of development, but I want to assure you that there are many resources available to help you design the studies necessary to satisfy FDA's regulatory requirements for your device. One of the best resources to start with is FDA's guidance on IVDs." Johnson handed out copies of the "In Vitro Diagnostic (IVD) Device Studies—Frequently Asked Questions" guidance to the group.

"Per Section III.2 of this guidance, a device is likely to be

exempt from most provisions of the Investigational Device Exemption (IDE) regulation, if it fits all of the following criteria:

1. The device is properly labeled in accordance with 21 CFR Part 809.10(c).
2. The device is noninvasive.
3. The device does not require an invasive sampling procedure that presents significant risk.
4. The device does not by design or intention introduce energy into a subject.
5. The device is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

"So, your device is exempt from most IDE requirements under 21 CFR Part 812.2(c)(3). However, keep in mind that the goals for your IVD studies are the same as for any other device studies. Therefore, FDA recommends that you (the sponsor) and the investigators conduct studies to produce valid scientific evidence demonstrating reasonable assurance of the safety and effectiveness of IgTope. And to receive clearance to market your device through a 510(k), you will have to perform the appropriate analytical performance and clinical testing.

"Specifically, since you are studying an IVD device that uses a well-characterized technology and has an intended use that falls within a type of device previously classified as Class II," Johnson continued, "the study should consist of a comparison of analytic performance of IgTope to Hevylite®-K132555, the legally marketed predicate. Over the next few weeks, we'll focus on designing a plan for your analytical performance validation studies. We can discuss any necessary clinical study requirements at a later date."

"After you've worked with Dr. Johnson, we'll help you seek preliminary feedback on your studies through a Q-sub[1] request to FDA," said Watson. "This will help you save time and funds."

Wrapping up, Johnson reassured Morales and her team. "This may sound like a lot of work now, but we can help you along the way with determining sample sizes and other important parameters for testing. And as Mr. Watson mentioned, FDA is available to provide feedback to help ensure that patients in the U.S. have first access to high-quality, safe, and effective medical devices of public health importance.[2] We'll help you engage with FDA as we work on your study designs."

[1]Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff (Pre-Sub guidance)

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdfm

[2]CDRH Vision and Mission

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/ucm300639.htm

Seeking FDA Feedback Through a Pre-Sub

After hammering out their study design with the aid of Dr. Johnson, Morales and her team regrouped with Watson, Johnson, and Pans.

"It looks like you have laid out some solid initial plans for the analytical performance validation studies required for your 510(k) submission," Watson began.

"Yes, the aid of Dr. Johnson was invaluable," Morales smiled.

Pleased, Watson replied, "I am glad to hear it. Now, as I mentioned in our last meeting, I recommend submitting a Pre-Submission, or Pre-Sub request, to seek feedback from FDA on key components of your study design before diving into testing."

"I believe last time you used the term Q-sub," Morales interrupted, slightly confused. "Is there a difference between a Q-sub and a Pre-Sub?"

"There is a slight difference, although the two terms are sometimes used interchangeably," Watson responded. "I'll let Ms. Pans, our Q-sub guru, explain."

"Like Mr. Watson said, there is a slight difference," Pans began. "To give you a little background: the Pre-Sub program began in 1995

when FDA established a pathway to obtain preliminary feedback on IDEs prior to submission. At the time, it was called the Pre-IDE program due to its limited focus. Due to the success of the Pre-IDE program, FDA expanded it to other types of premarket submissions such as

- Premarket Approval (PMA) applications
- Humanitarian Device Exemption (HDE) applications
- Evaluation of Automatic Class III Designations (*de novo* requests)
- Premarket Notification [510(k)] Submissions
- Clinical Laboratory Improvement Amendments (CLIA) Waiver by Application
- Certain Investigational New Drug Applications (INDs)
- Biologics License Applications (BLAs)

"Today, Pre-Subs are part of the more generic group of feedback requests commonly referred to as Q-Subs." Pans handed Morales and her team a printout. "This table describes the general features of a Pre-Sub and the other types of Q-subs (Table 2). FDA's guidance on Pre-Subs delves further into the differences."

"I see," Morales responded. "Thanks for clarifying."

Table 2: Comparison of Various Types of Q-Sub Requests

Type of Q-Sub	Type of Feedback or Information Provided	Meeting as Method of Feedback?	Typical Timeframe for Feedback
Pre-Submission (Pre-Sub)[1]	Guidance on product development and/or a future IDE, IND, or marketing submission. This includes specific questions regarding review issues relevant to a planned IDE, IND, or marketing application.	Upon request	75–90 days[2]
Informational Meeting	Presentation of information from a sponsor to educate FDA about ongoing device development or planned submissions without a specific request for feedback.	Yes	90 days
Study Risk Determination	Determination of whether a proposed device study is exempt from or subject to the IDE Regulation.[3] For device studies that are subject to the IDE regulations, FDA will also provide its determination of whether the study is a significant risk or non-significant risk study in response to a voluntary request for this information.	No	N/A
Early Collaboration Agreement Meeting	Direction on specified elements of a proposed study design.[4]	Yes	30 days or within agreed timeframe
Early Collaboration Determination Meeting	Determination of the type of clinical trial needed to provide evidence of effectiveness.[5]	Yes	Date for meeting agreed upon within 30 days
Submission Issue Meeting	Clarification of FDA requests for additional information to better ensure that a sponsor's formal response to FDA's request will fully address the outstanding questions.	Yes	21 days
Day 100 Meeting	Review of the status of a submitted PMA application.[6]	Yes	100 days (from PMA filing date)

Adapted from "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff"
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

[1]As defined in the MDUFA III Commitment Letter
[2]21 days for urgent public health issues
[3]21 CFR Part 812
[4]Section 520(g)(7) of the FD&C Act
[5]Section 513(a)(3)(D) of FD&C Act
[6]Section 515(d)(3) of the FD&C Act

Feedback on Pre-Subs Represent FDA's Best Advice on the Information You Provide

Pans continued. "Before we get started on the submission, it's important to note that while FDA's response to a Pre-Sub can be very useful, the feedback on a Pre-Sub represents FDA's best advice based on the information you provide. There are circumstances that could lead FDA to change their original opinion in the Pre-sub during a formal submission, such as[3]

- Information in the subsequent submission is not consistent with that contained in the Pre-Sub (e.g., change in proposed indication for use or device design)
- Data in the subsequent submission raise important new issues related to safety and effectiveness (e.g., a study is conducted as recommended by FDA, but results raise new safety concerns)
- Feedback given previously did not adequately address important new issues materially relevant to a determination of safety or effectiveness that have emerged since the time of the Pre-Sub (e.g., new alternative therapies/diagnostics have emerged since discussion of the clinical protocol, making the previously recommended study design unethical)."

[3]Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff

"Good to know, we will keep this in mind," said Morales.

What to Include in Your Pre-Sub Package

Morales transitioned to another line of thought, "I assume that FDA reviewers are extremely busy. However, we want to make sure that we include enough information to get the most accurate feedback possible. What and how much information should we include in our Pre-Sub?"

"You can check the 'Recommended Information for Pre-Sub Packages,' section of the Pre-Sub guidance for help with that," Watson responded. "And here are two checklists an FDA reviewer would use to see if your Pre-Sub request is complete. (Appendix C and Appendix D)

"This guidance contains recommendations for Pre-Subs regarding specific questions. There are also a number of general items that a Pre-Sub should contain. For example, a description of the device that includes sufficient information for a reviewer to understand what the proposed device is and how it works, and the proposed intended use/indications for use for the device."

Continuing to run down the Pre-Submission checklist, Watson added, "You haven't had any previous discussions with or submissions to FDA prior to this point, so you don't have any applicable submissions that need to be included. But you are far enough along in your plans that I suggest you include an overview of planned product development, including an outline of any nonclinical and clinical studies already completed, the analytical performance study plan you worked on with Dr. Johnson, and any specific questions you have related to that area."

"That's right," Johnson jumped in. "Specifically, you'll want to ask FDA:

- Questions regarding the analytical performance and study design protocols on the new instrument system
- How to deal with differences in platforms (e.g., relationship between cutoffs/medical decision points, reference ranges, measuring ranges) that might impact the method comparison outcomes
- What your sample selection (e.g., number of samples, inclusion/exclusion criteria for samples, statistical analysis of samples) should be for the method comparison and clinical comparison

Watson nodded in agreement. "Including protocol descriptions that are as detailed as possible will help you receive the most accurate feedback on these questions for your IVD device. For example, when explaining your precision study, you should specifically indicate your proposed number of samples, number of replicates, and your

acceptance criteria. When defining your samples, indicate the sample source (e.g., specialized testing clinic, university lab, hospital lab), if they were contrived, and how (e.g., diluted, spiked). Remember, FDA will be responding to your proposed studies, not designing the studies for you.

"In regards to your regulatory pathway of choice for the IgTope, you could ask FDA for feedback on the appropriateness of pursuing the 510(k) pathway and using Hevylite® as a predicate. In order to receive accurate feedback, you'll need to provide them with a comparison of the intended use and technological characteristics of IgTope and Hevylite® (Table 1) and, as appropriate, a proposed performance testing comparison study of the two devices. Again, remember that FDA will provide only high level comments on the appropriateness of a predicate."

"Earlier you mentioned that even though IgTope would be exempt from most provisions of the IDE regulation, we will still need to perform the appropriate clinical testing to receive clearance to market it through a 510(k). Will FDA be willing to discuss our device even though we don't have a clinical evaluation plan ready for their review?" Morales asked.
"Yes. FDA will work with you to provide feedback as you go. Since you're not ready to discuss the clinical evaluation yet, we'll just let them know that in the submission and send a follow-up Pre-Sub later," Watson responded.

Transitioning to the performance testing study design, Dr. Johnson explained, "Since your intended use focuses on monitoring a patient's condition over time, it will be important to perform your measurements on serial blood samples from patients previously diagnosed with MM. Using samples from patients with the disease will help you avoid any errors associated with testing healthy patients that may have measurements outside of your critical target range. These blood samples could be retrospective or prospectively collected samples, whichever you deem to be least burdensome. Serial samples should include an initial draw and I daresay a minimum of two sequential draws (a least three specimens per patient). Whether this number of samples is sufficient would be a good question to ask FDA in the follow-up Pre-Sub.

"It will also be critical to compare IgTope's findings to the predicate. An agreement comparison (i.e., method comparison study) should be made between IgTope and the predicate, for IgGκ, IgGλ, and the ratio of the two. As part of this comparison, you should calculate the positive percent agreement, negative percent agreement, and overall percent agreement between the two systems. Furthermore, a 95% confidence interval would be useful as well.

"Finally, I want you to be aware that if you ever want to change the intended use of IgTope to act as a diagnostic, you will likely need to conduct additional clinical trials for the new indication to test whether IgTope can distinguish a diseased sample from healthy samples. A modification to the intended use would also require a new 510(k) submission or perhaps a PMA, depending on the indication for use," Johnson concluded.

The more she heard, the happier Morales was that she and her team had come to the consultants for guidance during this critical portion of their product development.
"This is great advice. Based on your feedback, I think we'll submit two separate Pre-Subs for IgTope: the first one will focus on the intended use, general inquiry about the data requirements to support the indications for use, and questions related to analytical performance testing. Then the follow-up Pre-Sub can be dedicated exclusively to clinical testing."

"Sounds like a solid plan!" Watson responded. Ig Medical was ready to prepare its first Pre-Sub request. (Exhibit 2)

Maximizing the Benefit from your Pre-Sub Meeting

After compiling the necessary information for their request, Ig Medical met with the consultants

EXHIBIT 2: A PRE-SUB REQUEST

The Submission:

1. Prepare the required electronic (eCopy) and hard copy of the Q-sub documentation[1, 2]
2. Prepare a cover letter with the following information:
   - Identification of the Q-Sub type as described in Table 2 (i.e., Pre-Sub, Submission Issue)
   - Sponsor contact information
   - Device name
   - Information specific to the Q-Sub type (Appendices B–D of the Pre-Sub guidance)
   - Preferred method of feedback
3. Submit eCopy and hard copy Pre-Sub request to FDA

Post-Submission:

1. FDA conducts acceptance review (14 days): Acceptance Checklist (Appendix C of the Pre-Sub guidance) used to determine if the request meets the definition of the identified Q-Sub type and if a qualifying request is administratively complete.
   - Submission meets the definition of a Pre-Sub, informational meeting request, or a submission issue meeting request: FDA applies the relevant section of the Acceptance Checklist to ensure the submission is administratively complete and prepares the request response.
   - Submission contains insufficient information to determine the type of feedback requested: FDA designates the submission as "Refuse to Accept" (RTA), and notifies the applicant in writing that the submission has not been accepted and the reasons why.
2. If a meeting or teleconference is requested:
   - FDA works with sponsor to schedule the meeting/teleconference (21 days)
   - FDA provides preliminary feedback via email (at least 3 days prior to the meeting/teleconference)
3. FDA provides feedback (typically 75–90 days)
4. If a meeting or teleconference is held:
   - Sponsor provides draft minutes to FDA (15 days)
   - FDA reviews/edits minutes (30 days)
   - Minutes are finalized by sponsor and FDA

[1]Section 745(A)(b) of the FD&C Act
[2]eCopy Program for Medical Device Submissions
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf

once more before submitting their Pre-Sub.

Pans jumped right in. "Since you want to have a direct meeting or teleconference with FDA, typically we would have a maximum of 90 days before your Pre-Sub meeting is scheduled. I think it's important for us to go over some information about how you can best interact with FDA to prepare you.

"First, remember that FDA does not recommend iterative meetings on the same topic, so you need to make the most of this meeting," said Pans. "The discussion will most likely focus on your major questions submitted as part of the Pre-Sub package concerning your current stage in the device development and testing process. Pre-Sub meetings can also serve as a way to ask a few additional questions to gain clarification regarding FDA's written feedback about your path. Decide some focus points for the meeting, and then submit your questions to the lead reviewer at FDA. I suggest developing a written agenda and passing it along for feedback as well. FDA reviewers have extensive experience with these types of

meetings and may suggest other points for discussion that would be helpful from their end or that we may have overlooked."

"If only everyone who tried to schedule an important meeting with me would follow the same practice!" Morales lamented jokingly. "Do you have any others suggestions for us?"

"Always," Watson chuckled. "I must reiterate the importance of not expecting the meeting to serve in place of a formal clearance or FDA's approval programs. During this Pre-Submission meeting, FDA will not

- Make guarantees or binding commitments
- Hold to informal feedback provided years ago
- Approve a study design
- Clear/approve a device at the meeting
- Act as a consultant on the project

"Second, it is crucial to bring the right experts to the meeting to help you execute your objectives. Review your personnel and make sure the subject matter experts are in attendance. I would also suggest bringing a dedicated attendee to take notes for you. At the close of the meeting, I always find it useful to summarize action items and ask for clarification if needed. That way you make sure that both you and FDA are on the same page about what was discussed at the Pre-Sub meeting."

"We will have to make sure all of this is in our outline so we don't forget anything," said Morales. Looking over her notes on the Pre-Sub Submission and Feedback process (Exhibit 2), she stated, "I see that after the meeting we are supposed to submit meeting minutes to FDA."

Pans fielded that one. "Yes, sponsors submit draft minutes to FDA within 15 days. The minutes should reflect a summary (not a transcript) of the meeting discussion, and FDA would prefer that new responses to the FDA feedback provided during the meeting not be included in these minutes. However, that doesn't mean you should just ignore the feedback given at the meeting. FDA reviewers will use the minutes to document any recommendations that they have given, so they will be expecting that their feedback is taken into account in any future submissions or interactions."

"You said that the minutes that we submit are only a draft. Do we need to finalize the minutes at a later point or is this something FDA handles?" Morales asked.

"After you submit the draft minutes, FDA will review them and edit as they see necessary. If no changes are made, your submitted minutes will be considered final and you will be notified. But if FDA makes any changes, they will send the edits to you and you can approve them if you agree with the changes and no further follow-up is necessary. If you don't agree, you can file a 'minutes disagreement amendment' with FDA."

"So what happens if we do disagree? How does the disagreement get resolved?"

"Then you'll have 15 days from the time FDA notifies you of the edits to file the disagreement amendment," Pans explained. "FDA will arrange a teleconference to discuss, and at the conclusion, they will revise the minutes to reflect any resolution that was reached or note that the parties 'agree to disagree.' At this point, the minutes (as revised based on the teleconference) will be considered final."

"If you have any new questions or if there are areas that are still unclear, you may request further feedback as a Pre-Sub supplement," Watson added. "So do you have any further questions?"

"No, I think this is a good place to stop," Morales looked at her team for confirmation. "We're ready to submit the Pre-Sub with the help of Ms. Pans, and we will let you know when we arrange the meeting with FDA. It would be great if you could look over our meeting agenda and questions before we send them to the FDA reviewer. And of course, we would love to have the three of you attend the meeting. Your expertise has been invaluable and we cannot thank you enough!"

"It will be our pleasure," Watson smiled.

APPENDIX A: MULTIPLE MYELOMA

Multiple myeloma (MM) is a form of cancer that starts in the plasma cells (which produce antibodies) within bone marrow. The exact cause of MM is not clear. Past treatment with radiation therapy increases the risk of this type of cancer. MM primarily affects older adults.

MM is the second most common blood cancer in the United States, accounting for roughly 1 percent of all new cancers. Overall 24,050 new cases are expected in the U.S. in 2014 with a median survival of 45 to 60 months.

Symptoms include:

- Low red blood cell count (anemia), which can lead to fatigue and shortness of breath
- Low white blood cell count, which makes you more likely to get infections
- Low platelet count, which can lead to abnormal bleeding
- Bone or back pain, most often in the ribs or back, as the cancer cells grow in the bone marrow
- Weakened bones
- Broken bones (bone fractures) resulting from normal activities
- Pressure on spinal nerves if cancer grows in the spine bones, which can lead to numbness or weakness of the arms or legs

Traditional diagnostic and screening exams for Multiple myeloma include:

- Blood tests
- Albumin level
- Calcium level
- Total protein level
- Kidney function blood tests
- Complete blood count (CBC)
- Blood and urine tests to identify proteins, or antibodies (immunofixation)
- Blood tests to quickly and accurately measure the level of immunoglobulins (nephelometry)
- Bone X-rays may show fractures or hollowed out areas of bone. If your doctor suspects this type of cancer, a bone marrow biopsy will be performed.
- Bone density testing may show bone loss

Treatment for MM isn't always necessary. If you're not experiencing signs and symptoms, you may not require treatment. If signs and symptoms develop, a number of treatments can help control MM, including chemotherapy, corticosteroids, stem cell transplantation, and radiation therapy.

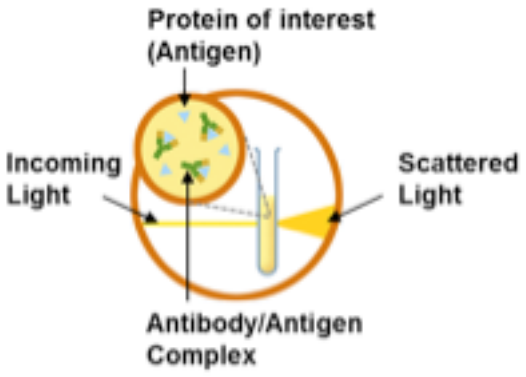
Sources: "Multiple Myeloma." Mayo Clinic.
http://www.mayoclinic.org/diseases-conditions/multiple-myeloma/basics/definition/con-20026607 (accessed 2015-02-13)
"Multiple Myeloma." American Cancer Society.
http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-key-statistics (accessed 2015-02-13)

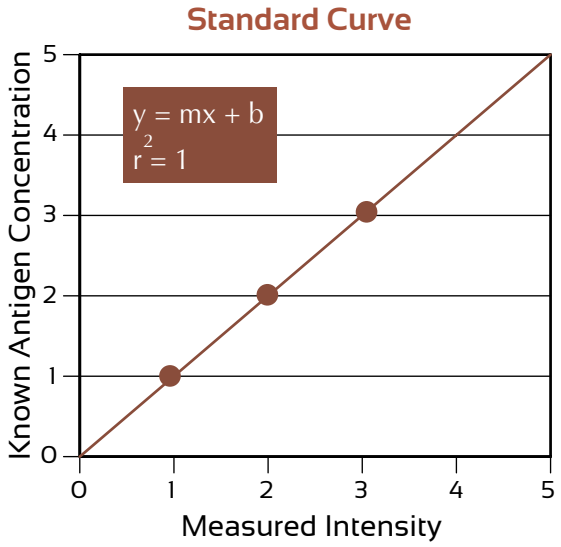
APPENDIX B: NEPHELOMETRY

Nephelometry is a method for determining the amount of cloudiness, or turbidity, in a solution by measuring the transmission and scattering of light passed through the solution. If a beam of light is passed through a turbid sample, scattering reduces the light's intensity. The exact quantity of light scattered is dependent upon the concentration and size distribution of the particles. In nephelometry, the intensity of the scattered light is measured. In turbidimetry, the intensity of light transmitted through the sample is measured.

In medicine, Nephelometric and turbidimetric measurements are often used to determine the quantity of specific proteins, such as immunoglobulin, found in blood or urine. However, measurement of specific proteins can be made difficult by the presence of other contaminating molecules. To improve the detection of a protein of interest that is in low concentration, it is often useful to measure a larger complex composed of the protein of interest combined with another molecule (such as a commercially available antibody specific to the protein of interest).

When the patient serum or urine has been mixed with the commercial antibodies, a light source is passed through the solution and sensitive detectors determine how much light is scattered by the presence of immune complexes in suspension. More immune complexes will form in the solution with an increasing amount of the protein in serum. Therefore, the increase in light scatter is indicative of higher levels of protein. The exact amounts can be determined by comparing with the light scatter from solutions of known protein concentration using a standard curve.





Source: "Nephelometry and turbidimetry." Encyclopedia Britannica.
http://www.britannica.com/EBchecked/topic/409243/nephelometry-and-turbidimetry

APPENDIX C: Q-SUBMISSION ACCEPTANCE CHECKLIST

Criteria	Yes	No
1. Has the type of Q-Sub been identified in the cover letter or has sufficient information been provided in the submission to identify the type of Q-Sub? Choices are: a. Pre-Submission (Pre-Sub) b. Informational Meeting request c. Submission Issue Meeting request d. Early Collaboration Meeting request (includes both Agreement and Determination Meetings) e. Study Risk determination request Note: this checklist is not needed for PMA Day 100 Meeting requests	**Continue with question 2**	**Recommend Refuse to Accept**
2. Did the sponsor correctly identify the type of Q-Submission based on the definitions below? If not, can you determine the correct type of Q-Submission based on the definitions in 2a below?	**Go to the checklist specific to that Q-Sub type (see question 3 below)**	**Go back to question 1 and answer "no"**

2a. Definitions

Pre-Submission (Pre-Sub)

- ✓ To guide product development and/or a future IDE, IND, or marketing submission
- ✓ Includes specific questions regarding review issues relevant to a planned IDE, IND, or marketing application

Informational Meeting Request

- ✓ To provide an overview of ongoing device development when there are one or more submissions planned within the next 6 to 12 months; to familiarize reviewers about new device(s) with significant differences in technology from currently available devices; or to otherwise provide information to FDA that the Agency may find useful
- ✓ Contains NO requests for FDA feedback

Submission Issue Meeting Request

- ✓ To discuss an active (i.e., under review or on hold) IDE, IND, or marketing submission for which FDA requested additional information related to that submission

Early Collaboration Meeting—Agreement Meeting

- ✓ To get the Agency's agreement on specified elements of a proposed study design [as outlined in the FD&C Act 520(g)(7)]

Early Collaboration Meeting—Determination Meeting

- ✓ To get the Agency's determination of the type of clinical trial needed to provide evidence of effectiveness [as outlined in the FD&C Act 513(a)(3)(D)]

Study Risk Determination

- ✓ Requests FDA's feedback on whether a planned study is a significant risk (SR) study, a non-significant risk (NSR) study, or exempt from IDE, or generally whether a planned study requires an IDE

APPENDIX C: Q-SUBMISSION ACCEPTANCE CHECKLIST CONTINUED

3. Q-Sub type determined to be:
   - ☐ Pre-Submission (go to Pre-Sub checklist—Appendix C or page 50 of the Pre-Sub guidance)
   - ☐ Informational Meeting Request (go to Informational Meeting checklist—Appendix D or page 52 of the Pre-Sub guidance)
   - ☐ Submission Issue Meeting Request (go to Submission Issue Meeting checklist—Appendix E or page 53 of the Pre-Sub guidance)
   - ☐ Agreement Meeting Request (follow existing practices as described in "Early Collaboration Meetings Under the FDA Modernization Act [FDAMA]: Final Guidance for Industry and for CDRH Staff")
   - ☐ Determination Meeting Request (follow existing practices as described in "Early Collaboration Meetings Under the FDA Modernization Act [FDAMA]: Final Guidance for Industry and for CDRH Staff")
   - ☐ Study Risk Determination (follow existing practices as outlined in "Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Significant Risk and Non-significant Risk Medical Device Studies")

Source: Appendix 2: Q-Sub Acceptance Checklist. "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" guidance, pg. 47
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

APPENDIX D: PRE-SUBMISSION CHECKLIST

Pre-Submission includes:	Yes	N/A	No
1. Cover letter with contact information for sponsor and name of subject device.			
2. Table of Contents			
3. Device description includes information sufficient to understand what the proposed device is and how it works, such as: ✓ A description of the device in text and with pictures, diagrams, and/or engineering drawings, as applicable; ✓ An explanation of the mechanism of action (i.e., how the device achieves its intended output or effect); ✓ Characteristics of the device output (if applicable); ✓ Description of the materials used in the device; ✓ For an IVD, detailed technical description of the device including instruments, reagents, components, software, principles of operation, and accessories; ✓ An explanation of the scientific basis for the device and/or the expected clinical utility; and ✓ For a device to be submitted in a 510(k), any anticipated predicate and a comparison of the device to the predicate device. **OR** ✓ A specific reference to a prior submission (e.g., Pre-Sub, Pre-IDE) where this information was previously provided and a statement that the information has not changed. *See the Pre-Sub guidance for additional items that may be appropriate in the device description. (Note that inclusion of every item in the guidance is not required to accept the submission, only sufficient information to have a basic understanding of the device in question so that FDA's review can begin. More detailed information can be requested interactively.)*			

APPENDIX D: PRE-SUBMISSION CHECKLIST CONTINUED

Pre-Submission includes:	Yes	N/A	No
4. Proposed intended use/indications for use, which may include: ✓ Identification of the disease or condition the device is indicated to prevent, mitigate, screen, monitor, treat, or diagnose; ✓ Identification of the target population; ✓ Part of the body or type of tissue to which applied or with which the device is interacting; ✓ Frequency of use; ✓ Physiological use; ✓ Statement of whether the device is intended for prescription and/or over-the-counter use; and ✓ If an IVD device, includes a detailed draft of the intended use of the device including the intended use population, the analyte/condition to detect, and the assay methodology. **OR** ✓ A specific reference to a prior submission (e.g., Pre-Sub, Pre-IDE) where the indication for use was previously provided and a statement that it has not changed.			
5. A summary of any previous discussions or submissions (with submission number[s]) regarding the same device, if applicable			
6. An overview of planned product development, including an outline of nonclinical and clinical testing either planned or already completed			
7. Specific questions for FDA feedback regarding review issues relevant to a planned IDE, IND, or marketing application			
8. Desired method for feedback			

Did you check "yes" or "N/A" for all of the items in a white box (i.e., not shaded)?

- ☐ Yes. Recommend Acceptance (RTAA). If one or more of the shaded items are missing, contact the sponsor by phone or email to request this additional information (which can be added to the review record electronically).
- ☐ No. Recommend Refuse to Accept (RTA).

Source: Appendix 2: Pre-Submission Checklist. "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" guidance, pg. 50
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

GLOSSARY

Approval: Approval of a medical device [or clearance for devices subject to 510(k), see below] must be obtained from the FDA by demonstrating that the device is reasonably safe and effective, and that the benefits outweigh the risks for the intended patient population before it can be put into commerce. The term "approval" is generally used in the context of premarket approvals for Class III medical devices.

Clearance: Clearance of a medical device not exempt from 510(k) must be obtained from the FDA by demonstrating that the device is substantially equivalent (SE) to its predicate device before the device is put into commerce.

Clinical Investigation (Trial or Study): A systematic investigation conducted to evaluate the safety and effectiveness of a medical device using human subjects or specimens.

Clinical Laboratory Improvement Amendments (CLIA): The Clinical Laboratory Improvement Amendments (CLIA) regulate laboratory testing and require clinical laboratories to be certificated by their State as well as the Center for Medicare and Medicaid Services (CMS) before they can accept human samples for diagnostic testing. Laboratories can obtain multiple types of CLIA certificates, based on the kinds of diagnostic tests they conduct.

Three Federal Agencies are responsible for CLIA: The FDA, CMS, and the Centers for Disease Control and Prevention (CDC).

Current Good Manufacturing Practices (cGMP): Production and testing practices that help ensure safe, effective, and quality products. In the United States, cGMP Regulations are promulgated by the FDA under the authority of the FD&C Act (Chapter IV for food; Chapter V, Subchapters A, B, C, D, and E for drugs and devices). The "c" stands for "current," reminding manufacturers that they must employ up to-date technologies and systems to comply with the regulation. It is the manufacturers' responsibility to be current.

Device Classification: The Food and Drug Administration (FDA) has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The three classes and the requirements which apply to them are:

1. Class I General Controls
   - With Exemptions
   - Without Exemptions
2. Class II General Controls and Special Controls
   - With Exemptions
   - Without Exemptions
3. Class III General Controls and Premarket Approval

De Novo Classification: New devices that FDA has not previously classified based on risk are "automatically" or "statutorily" classified into Class III by operation of Section 513(f)(1) of the FD&C Act, regardless of the level of risk they pose.

To limit unnecessary expenditure of FDA and industry resources that could occur if lower risk devices were subject to Premarket Approval (PMA) under Section 515 of the FD&C Act, Congress enacted section 513(f)(2) of the FD&C Act as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA). The process created by this provision, which is referred to in FDAMA as the Evaluation of Automatic Class III Designation, is referred to as the "*de novo* process."

The *de novo* process enables a submitter to request the FDA to make a risk-based classification determination for a device. If the *de novo* request is granted, the device is placed into Class II or Class I, and a new regulation is created. The device may then be marketed immediately and can serve as a predicate device for future 510(k)s.

If the *de novo* request is declined, the device remains in Class III and will require a PMA prior to going to market.

Different Technological Characteristics: As defined in Section 513(i)(1)(B) of the FD&C Act [21 U.S.C. § 360c(i)(1)(B)], devices are deemed to have different technological characteristics when there is a significant change in the materials, design, energy source, or other features between the two devices.

Effectivenesss: There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. [21 CFR Part 860.7(e)(1)]

General Controls: General controls include the following:

- Establishment Registration of companies required to register under 21 CFR Part 807.20, such as manufacturers, distributors, repackagers, and relabelers
- Medical Device Listing with FDA of devices to be marketed
- Manufacturing devices in accordance with cGMP in 21 CFR Part 820 (Quality System Regulation)
- Labeling devices in accordance with labeling regulations in 21 CFR Part 801 or 809
- Submission of a Premarket Notification, or 510(k), before marketing a device

For additional information please refer to: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/General and SpecialControls/default.htm

Good Clinical Practices (GCP): A set of guidelines that must be followed when conducting clinical trials to ensure that the rights and well-being of the trial participants are protected and that the data generated in the trial is valid. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials involving human participants. The guidelines were developed in order to provide drug clinical trials with a unified standard across the European Union, Japan, and the United States and were labeled ICH-GCP at the International Conference on Harmonization (ICH), 1996. For medical devices, ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects–Good Clinical Practice was developed and is the global standard for medical device GCP.

Good Guidance Practices (GGP): FDA's policies and procedures for developing, issuing, and using guidance documents. Please refer to the following links for additional information:

- 21 CFR Part 10.115

  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=10.115
- Food and Drug Administration Report on Good Guidance Practices: Improving Efficiency and Transparency

  http://www.fda.gov/downloads/AboutFDA/Transparency/TransparencyInitiative/UCM285124.pdf

Good Laboratory Practices (GLP): A set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported, and archived. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

Guidance Documents: Documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Draft guidance documents are for the public to comment on and suggest changes for, but are subject to change and are not for implementation. [See 21 CFR Part 10.115 (b), (d), and (g)]

Immunoglobulin: Immunoglobulins are glycoprotein molecules that are produced by plasma cells in response to an immunogen and that function as antibodies. The immunoglobulins derive their name from the finding that they migrate with globular proteins when antibody-containing serum is placed in an electrical field.

In Vitro: Outside the living body and in an artificial environment.

In Vitro Diagnostic (IVD): Those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. IVD products are devices as defined in Section 201(h) of the FD&C Act and may also be biological products subject to Section 351 of the Public Health Service Act. The regulatory definition of in vitro diagnostic products is found in 21 CFR Part 809.3(a).

Intellectual Property: Intellectual property (IP) rights are the legally recognized exclusive rights to creations of the mind. Common types of intellectual property rights include copyright, trademarks, patents, industrial design rights, trade dress, and in some jurisdictions trade secrets.

Intended Use/Purpose: Intended use means the general purpose of the device—or what the device does. The intended use of a device is the general purpose of the device or its function (not to be confused with the indications for use, or IFU, of the device).

The IFU is the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended. By definition, the intended use of a device encompasses the IFU.

Investigational Device Exemption (IDE): IDE refers to the regulations under 21 CFR Part 812, a regulatory submission to study a medical device in human subjects. IDEs are only required for studies performed in the United States. An IDE allows an investigational device to be used in a clinical study to collect the safety and effectiveness data required for a marketing application. However, it is to be noted that IDEs are also often required for studies that are not being conducted to support a marketing application.

Medical Device: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, "or accessory" that is the following:

1. Recognized in the official National Formulary, the United States Pharmacopeia, or any supplement to them
2. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals
3. Intended to affect the structure or any function of the body of man or other animals
4. Does not achieve its primary intended purposes through chemical action within or on the body of a human or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes [Section 201(h) of the FD&C Act]

Nonclinical Investigation: A systematic investigation conducted to evaluate the safety and effectiveness of a medical device using non-human subjects or specimens, primary or secondary cell lines, or computational models.

Premarket Approval (PMA): The FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Any Premarket Approval application for a Class III medical device, including all information submitted with or incorporated by reference therein (21 CFR Part 814.3). Class III devices are those that cannot be classified as Class I or Class II devices because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and either (1) are purported to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health; or (2) present a potential unreasonable risk of illness or injury.

Premarket Notification—510(k) Clearance: Section 510(k) of the FD&C Act requires device manufacturers, who must register, to notify FDA of their intent to market a medical device at least 90 days in advance. This is known as premarket notification—also called PMN or 510(k). This allows FDA to determine whether the device in question is equivalent to a device already placed into Class I, Class II, Class III requiring a 510(k), or a legally marketed preamendment device. Thus, "new" devices (not in commercial distribution prior to May 28, 1976) that have not been classified can be properly identified.

Specifically, medical device manufacturers are required to submit a premarket notification if they intend to introduce a device into commercial distribution for the first time or reintroduce a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected. Such change or modification could relate to the design, material, chemical composition, energy source, manufacturing process, or intended use.

Product Code: The device name and product code identify the generic category of a device for FDA. The product code assigned to a device is based upon the medical device product classification designated under 21 CFR Parts 862–892.

Quality Systems Regulation (21 CFR Part 820): Requirements related to the methods used in and the facilities and controls used for designing, manufacturing, packaging, labeling, storing, installing, and servicing of medical devices intended for human use.

Regulatory Pathways: Before a medical device can be put into the U.S. market, manufacturers of medical devices have to submit evidence to demonstrate product safety and effectiveness to the Office of Device Evaluation (ODE) and to the Office of In Vitro Diagnostic and Radiological Health (OIR) of the Center for Devices and Radiological Health (CDRH) at FDA. There are various submission processes and respective applications for evaluation. PMA, PMA Supplement, Product Development Protocol (PDP), Humanitarian Device Exemption (HDE), IDE, IDE Amendment, IDE Supplement, and 510(k) are programs administered by ODE and OIR. They are also called regulatory pathways.

Safety: There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks. [21 CFR Part 860.7(d)(1)]

Scientific Evidence: Evidence that serves to either support or counter a scientific theory or hypothesis. The strength of scientific evidence is generally based on the results of statistical analysis and the strength of scientific controls, for example, information from well-controlled clinical studies.

Significant and Non-Significant Risk Devices: A "significant risk device" presents a potential for serious risk to the health, safety, or welfare of a subject. These devices are either intended as an implant or are substantially important in diagnosing, curing, mitigating, or treating disease (e.g., dental lasers, embolization devices for urological use, collagen, and bone replacements). For a full definition of "significant risk device," refer to 21 CFR Part 812.3 (m).

A "non-significant risk device" does not pose a significant risk to the human subjects (e.g., external monitors for insulin reactions, general biliary catheters, MRIs within specified parameters).

Special Controls: Special controls may include, but are not limited to, the following:

- Special labeling requirements
- Mandatory performance standards
- Postmarket surveillance
- Nonclinical and/or clinical testing
- Other specific types of performance testing

For additional information please refer to: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm

Sponsor: As defined in 21 CFR Part 812.3 (n), a sponsor means a person who initiates, but who does not actually conduct, the investigation. That is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. For definitions of related terms please refer to 21 CFR Part 812.3.

Substantial Equivalence: As part of the 510(k) process, FDA may issue an order of substantial equivalence if it determines that, as compared to the legally marketed predicate device, the new device has the same intended use and the same technological characteristics as the predicate, or it has the same intended use and different technological characteristics, and the different technological characteristics do not raise different questions of safety and effectiveness.

STUDENT ACTIVITIES

SESSION 1

I. Review the following materials before Session 1:

1. Information on Multiple Myeloma, Immunoglobulins, and Nephlometry
   a. Mayo Clinic: Multiple Myeloma
      http://www.mayoclinic.org/diseases-conditions/multiple-myeloma/basics/definition/con-20026607
   b. American Cancer Society: Multiple Myeloma
      http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-key-statistics
   c. Structure and Function of Immunoglobulins
      http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3670108/pdf/nihms469957.pdf

d. Nephelometry and Turbidimetry

http://www.britannica.com/EBchecked/topic/409243/nephelometry-and-turbidimetry

2. CDRH Learn Materials

a. Webinar audio file: "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff"

http://www.fda.gov/downloads/Training/CDRHLearn/UCM387649.wmv

b. Slides

http://www.fda.gov/downloads/Training/CDRHLearn/UCM387291.pdf

c. Transcript

http://www.fda.gov/downloads/Training/CDRHLearn/UCM387646.pdf

3. Mandatory Reading

a. Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

b. Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies—Frequently Asked Questions

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071230.pdf

4. Optional Reading

a. Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm

b. The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] Guidance for Industry and Food and Drug Administration Staff

http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm284443.pdf

c. eCopy Program for Medical Device Submissions

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf

d. Video: How to Create and Submit an eCopy

(Approximately 27 minutes)

http://www.accessdata.fda.gov/cdrh_docs/presentations/eCopy/index.html

II. Answer the following questions before Session 1—Fundamental concepts:

1. Describe the following items for the IVD device discussed in the case study:
   a. Device Description
   b. Proposed Intended Use
   c. Indications for Use
2. Using the Pre-Sub Guidance, answer the following:
   a. What is a Pre-sub?
   b. Name three types of Q-subs and describe what they are.

SESSION 2

I. In-class discussion (instructor guidance required):

1. Discuss the different types of Q-Sub requests:
   a. Pre-Submission (Pre-Sub)
   b. Informational Meeting
   c. Study Risk Determination
   d. Early Collaboration Meeting
   e. Submission Issue Meeting
   f. Day 100 Meeting
2. Discuss the requirements for an IVD Pre-Sub request.

   Refer to Appendix 1F "Pre-Sub for an IVD" in the "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" guidance

SESSION 3: PROJECT AND PRESENTATION

Note: This project may be used to satisfy, in part, a senior or graduate project or other special academic requirement.

I. Review the following material before beginning the project:

Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

II. Prepare a Pre-Submission Team Project

1. Prepare a Pre-Submission for a 510(k) medical device. This device can be one you have focused on in class, the IgTope device discussed in the case study, or a device of your choice.

   The following sections should be included in your project as recommended by the Pre-Sub guidance:
   a. Cover Letter
   b. Table of Contents
   c. Device Description
   d. Proposed Intended Use/Indications for Use
   e. Overview of Product Development
   f. Specific Questions to ask FDA
   f. Method for Feedback
2. Review Appendix 1 of the Pre-Sub guidance. Based on the information in Section C (page 35), list two to three criteria applicable to submitting a Pre-Sub for your medical device. Assume it is a Pre-Sub for a 510(k) device.